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A knowledge-informed chemotype approach to mining the ToxCast/Tox21 chemical-data landscape

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ToxCast and Tox21 chemical libraries currently exceed 2000 and 8000 unique chemicals, respectively, and span a broad diversity of chemical use-types, functionality, and toxicity mechanism and endpoint space. These libraries function as mechanism probes across hundreds of high-throughput in vitro bioassays. Structure-activity relationship (SAR) models and structure alerts that carry historical chemical-toxicity inferences can be projected onto this chemical landscape as a way of incorporating prior knowledge, thereby aiding in the detection of significantly enriched patterns and associations within and across the in vitro and in vivo data landscapes. A set of public ToxPrint chemotypes are being used to create a common platform for storing and communicating such associations, and for profiling and comparing structure inventories. Examples will be presented using such knowledge-informed features to convey associations within structure subsets pertaining to metabolic activation of rat carcinogens, disruption of mitochondrial membrane potential, and induction of cleft palate. The large and growing in vitro, in vivo, and computed property data profiles associated with ToxCast/Tox21 chemicals are also providing a means to expand the concept of molecular similarity beyond that of chemical structure alone, to build on prior knowledge and inform read-across approaches. Abstract does not reflect EPA, FDA, or NIH policy.

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